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EDITED BY N. RASHEVSKY

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A NOTE ON BIOLOGICAL PERIODICITIES

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The approximation method for solving diffusion problems is generalized to enable computation not only of the fundamental frequency, but also of higher harmonics in certain types of periodic solutions.

Following a suggestion by the author (Rashevsky, 1938; 1948a, chap. vi), Alvin M. Weinberg (1938) showed that diffusion phenomena in spherical cells may show periodicities when there are two interacting substances involved. Weinberg considered only solutions which possess central symmetry. The more general case was later studied by the author (Rashevsky, 1948b). Soon after the publication of his paper, A. Weinberg (1939) showed that essentially the same results may be obtained in a much more simple manner by the use of the approximation method (Rashevsky, 1940). This method, however, yields only the fundamental frequency of oscillations, whereas actually there is a discrete infinite number of possible frequencies. The purpose of this note is to show how the approximation method can be extended to give all possible frequencies.

The reason for the apparent failure of the approximation method to give all the frequencies can be readily seen. To each higher frequency there corresponds a distribution of concentration in the cell which fluctuates in space and has several maxima and minima. The approximation method, as used hitherto, presupposes essentially a monotonic, or almost monotonic, variation of concentration between the center and the periphery of the cell. It presupposes the same direction of flow of the metabolite at all points of any line joining the center to the periphery. If, however, there are maxima and minima of the concentrations in the cell, then the metabolite flows out of regions of high concentration into regions of low concentration. There are internal flows which are not all directed in the same way. Cases of purely internal flows, without exchange with the surrounding medium, have, however, been studied (Rashevsky, 1948a, chap. xix) in connection with polarity of spheroidal cells, by dividing the cell into two regions, and expressing the interchange of metabolites between

the two regions. This procedure may be generalized for the present case.

There is a discrete infinite number of periodical solutions (Rashevsky, 1948b), each characterized by an *eigenvalue* of the boundary problem and by a corresponding frequency. Each solution represents, in general, a highly complex distribution of concentrations which is highly asymmetric even for a spherical cell. Through proper combination of these solutions we can obtain practically any configuration of any complexity. To such a general configuration there will, however, correspond not one, but a large number of frequencies.

To apply the approximation method, we proceed as follows:

Subdivide the cell, which now does not need to be spherical, into N regions of arbitrary size and shape. The only limitation is that these regions fill the space of the cell densely. We again consider two substances. We denote the average concentration of the first substance in the ith region by $c_1^{(i)}$; that of the second by $c_2^{(i)}$. We again assume that the rate of production of the first substance is given anywhere by

$$q_1 = a_{11}c_1 + a_{12}c_2 , \tag{1}$$

and that of the second by

$$q_2 = a_{21}c_1 + a_{22}c_2 , \tag{2}$$

where a_{11}, a_{12}, a_{21}, and a_{22} are constants.

The inside diffusion coefficients are the same everywhere, and we denote them by D_{i1} and D_{i2}. We denote the outside diffusion coefficients by D_{e1} and D_{e2}. The outside concentrations are denoted by c_{01} and c_{02}.

A region R_i may be adjacent either only to other regions R_k, R_l, R_m; or partly to other regions, partly to the membrane of the cell. The permeabilities of the latter for the two substances shall be denoted by h_1 and h_2.

We now may write down the expression for the material balance of each region in exactly the same way as we do for a single cell (Rashevsky, 1940, 1948a). The only difference is that now, instead of a flow only in two directions, longitudinal and transverse, we shall have as many flows as the given region has adjacent regions. Thus for the first substance we shall find an expression of the form

$$\frac{dc_1^{(i)}}{dt} = a_{11}c_1^{(i)} + a_{12}c_2^{(i)} + \sum_k \lambda_{ik}(c_1^{(i)} - c_1^{(k)}) + \bar{\lambda}_i c_1^{(i)} - c_{01} , \tag{3}$$

where λ_{ik} are constants determined by the sizes and shapes of the ith region and of all the adjacent regions R_{k1} and the summation is extended over all the adjacent regions. The λ_{ik}'s also contain D_{i1} . The quantities $\bar{\lambda}_i$ appear only for such regions as are adjacent to the membrane of the cell and contain, beside the size and shape of the region, the quantity h_1 and D_{e1} . A similar equation holds for $c_2^{(i)}$.

If we write all the differential equations for all N regions, and if we put

$$c_1^{(1)} = x_1; \quad c_2^{(1)} = x_2; \quad c_1^{(2)} = x_3; \quad c_2^{(2)} = x_4 \cdots \text{etc.}, \tag{4}$$

we obtain a system of $M = 2N$ linear differential equations of the form

$$\frac{dx_p}{dt} = \sum_s A_{ps} x_s , \tag{5}$$

in which, in general, a number of A_{rs}'s are equal to zero. All the A_{rs}'s depend on the sizes and shapes of the different regions. Those sizes and shapes are determined in the usual way by the three overall dimensions $r_1^{(i)}$, $r_2^{(i)}$, and $r_3^{(i)}$. For each region we have, in general, the problem of the "triaxial cell" (Householder, 1942).

The secular equation

$$\begin{vmatrix} A_{11} - \nu & A_{12} & \cdots & A_{1M} \\ A_{21} & A_{22} - \nu & \cdots & A_{2M} \\ \cdots & \cdots & \cdots & \cdots \\ A_{M1} & A_{M2} & & A_{MM} - \nu \end{vmatrix} = 0 \tag{6}$$

will have, in general, M roots, some real, some complex. This means that the particular configuration is a composite one consisting of the superposition of several configurations with different *eigenvalues*. If equation (6) has only a pair of conjugate complex roots; or, which is infinitely improbable (Rashevsky, 1948b), two purely imaginary roots, that means that configuration is a "simple" one, corresponding to an *eigenvalue* in the exact treatment of the problem.

The important problem now is to determine such configurations for which equation (6) has only one pair of conjugate complex roots. For small values of N , and for simple arrangements, this is not too difficult. In general, however, the problem is not easy. For a fixed M , the coefficients A_{ps} are functions of the $3M$ quantities $r_1^{(i)}$, $r_2^{(i)}$, and $r_3^{(i)}$. The requirement that equation (6) has only a pair of conjugate complex roots leads to some relations between the coefficients A_{ps} , and thus to relations between the quantities $r_1^{(i)}$, $r_2^{(i)}$, and $r_3^{(i)}$.

Although we reduce the problem to a system of algebraic equations, because of the large number of variables it becomes rather unwieldy.

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A NOTE ON THE PROBABILISTIC APPROACH TO THE CANCER PROBLEM

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Assuming that the initiation of cancer growth is due to a purely accidental fluctuation of some physicochemical condition, it is possible to derive the equation for the cancer incidence as a function of age. The final result depends on whether it is assumed that a single accidental fluctuation in a cell is sufficient to produce cancer, or that a finite number, k, of repetitions of the accidental fluctuation must occur in the same cell. In principle it is possible to determine from observed incidence curves the number k. Actually, however, this cannot be done at present, because the difference of the theoretical curves for different k's is rather small, and the available cancer statistics are not accurate enough to show such differences.

In a previous paper (Rashevsky, 1945) we suggested the circumstance that every individual case of spontaneous cancer incidence seems to be determined by chance as a possible starting point for a mathematical theory of cancer. While we can predict with greater or lesser accuracy the incidence of cancer as a function of age or other variables in a large population, nothing can be predicted about each individual case. With this probabilistic concept as a starting point, and with the aid of an additional assumption about the interaction of two factors, a growth promoting one and a growth inhibiting one, we derived the equation for the variation of cancer incidence with age. This equation proved to be in good agreement with available data.

Whatever the physicochemical changes may be which result in a transformation of a normal cell into a cancer cell, it seems likely that these changes are of the nature of an accidental fluctuation. The purpose of this note is to show that regardless of the physicochemical mechanism involved, the notion of accidental fluctuation leads to some consequences which, in principle, may be tested experimentally, and inversely, that some conclusions as to the character of these fluctuations may be shown from appropriate observation.

Let us first consider the unrealistic abstract case of a uniform population of identical individuals. Let the probability that any one cell of the individual undergoes an accidental fluctuation which transforms it into a cancer cell at a time between t and $t + dt$ after birth be $p(t)\,dt$. We shall refer to such a fluctuation as "cancer fluctua-

tion." What is the probability that the individual will develop cancer for the first time at the age t?

Divide the time into equal small intervals Δt, numbered successively beginning from the time of birth. Let p_k be the probability of a cancer fluctuation during the kth interval. The probability of the cancer fluctuation not occurring during the kth interval is $1 - p_k$. The probability that a cancer fluctuation does not occur during the first $i - 1$ intervals, and occurs during the ith interval for the first time, is

$$P_{1i} = (1-p_1)(1-p_2)\cdots(1-p_{i-1})p_i . \tag{1}$$

Consider the product

$$K_{i-1} = (1-p_1)(1-p_2)\cdots(1-p_{i-1}). \tag{2}$$

If, as is usually the case, $p_k << 1$, we have

$$\log K_{i-1} = \sum_1^{i-1} \log (1-p_k) = -\sum_i^{i-1} p_k, \tag{3}$$

or

$$K_{i-1} = \exp\left[-\sum_1^{i-1} p_k \right]. \tag{4}$$

Introducing this into (1) we find

$$P_{1i} = p_i \exp\left[-\sum_1^{i-1} p_k \right]. \tag{5}$$

Now let the intervals tend to zero, their number increasing indefinitely. Then

$$p_i = p(t)\,dt, \tag{6}$$

and the sum in (4) and (5) tends to the integral

$$\int_0^t p(\tau)\,d\tau . \tag{7}$$

Hence, denoting by $P_1(t)\,dt$ the probability of a cancer fluctuation occurring for the first time between t and $t + dt$, we have from (5)

$$P_1(t)\,dt = p(t) \exp\left[-\int_0^t p(\tau)\,d\tau \right] dt . \tag{8}$$

In particular if

$$p(t) = p = (\text{constant}), \tag{9}$$

we find

$$P_1(t)\,dt = pe^{-pt}dt\,. \tag{10}$$

Thus for a constant $p(t) = p$, the incidence of cancer decreases monotonically with age.

Actually, for ages above 20 years, the incidence curve increases exponentially, and then at about the age of 60 years (Hoffman, 1915), the rate of increase declines. What can we conclude from this about the function $p(t)$? Suppose that $P_1(t)$ is given empirically. Then, shortening equation (8) by dt and taking logarithms, we have:

$$\log p(t) - \int_0^t p(\tau)\,d\tau = \log P_1(t)\,. \tag{11}$$

Differentiating (11) and rearranging, we find:

$$\frac{dp(t)}{dt} - p^2(t) = p(t)\,\frac{d}{dt}\log P_1(t)\,. \tag{12}$$

As observation seems to indicate, let

$$P_1(t) = Ae^{at}; \qquad \log P_1(t) = \log A + at\,, \tag{13}$$

where A and a are constants.

Introducing (13) into (12) we find:

$$\frac{dp(t)}{dt} = ap(t) + p^2(t)\,. \tag{14}$$

Integrating this with the initial condition for $t = 0$, $p(t) = p_0$, we find:

$$p(t) = \frac{p_0\,ae^{at}}{p_0 + a - p_0\,e^{at}}. \tag{15}$$

For $at = \log\,(p_0 + a)/p_0$, the function $p(t)$ becomes infinite.

Thus, if relations (13) hold, and if the occurrence of cancer is due to a single cancer fluctuation in a cell, the probability of such a fluctuation is given by (15).

We may, however, consider the more general possibility, namely, that a normal cell becomes a cancer cell after k accidental fluctuations occur in it. The first fluctuation would leave some kind of a trace which is enhanced by the subsequent fluctuations. Let us consider the simplest case, where the probability of a fluctuation is independent of whether any fluctuations occurred in the cell previously, and is equal to a constant p. The probability $P_1(t)\,dt$ now equals the product of the probability $p(t, k-1)$ that $k-1$, and only $k-1$, fluctuations

have occurred in the cell in the interval 0 to t, and that *one* fluctuation occurs between t and $t + dt$.

To compute $\mathbf{p}(t, k-1)$ we proceed as follows: Divide again the interval 0, t into n equal intervals. The probability of a fluctuation occurring within any interval is now

$$p_1 = p\Delta t. \tag{16}$$

The probability of the fluctuation occurring only $k-1$ times in the n trials is equal to

$$\mathbf{p}_n(k-1) = \frac{n!}{(k-1)!(n-k+1)!} p_1^{k-1}(1-p_1)^{n-k+1}. \tag{17}$$

Again let n increase indefinitely, Δt decreasing to zero. Then the expression $n!/(k-1)!\,(n-k+1)!$ tends to

$$\frac{n^{k-1}}{(k-1)!}, \tag{18}$$

and $\mathbf{p}_n(k-1)$ tends to $\mathbf{p}(t, k-1)$. The probability p_1 now becomes

$$p_1 = p\,dt. \tag{19}$$

The factor $(1-p\,dt)^{n-k+1}$ tends with increasing n to $(1-p\,dt)^n$, or, because of

$$n = \frac{t}{dt}, \tag{20}$$

to

$$\left(1 - \frac{pt}{n}\right)^n. \tag{21}$$

Put

$$-\frac{pt}{n} = \frac{1}{z}. \tag{22}$$

Then (21) becomes

$$\left(1 + \frac{1}{z}\right)^{-zpt} = \left[\left(1 + \frac{1}{z}\right)^z\right]^{-pt}. \tag{23}$$

As n increases, the absolute value of z increases also, and the right-hand side of (23) tends to e^{-pt}.

Expression (20) introduced into (18) gives

$$\frac{t^{k-1}}{(k-1)!\,(dt)^{k-1}} \tag{24}$$

while p_1^{k-1} becomes, because of (19):

$$p^{k-1}(dt)^{k-1}. \tag{25}$$

Hence, as n tends to infinity, $\mathbf{p}_n(k-1)$ tends to

$$\mathbf{p}(t, k-1) = \frac{1}{(k-1)!} p^{k-1} t^{k-1} e^{-pt}. \tag{26}$$

Therefore, we find for $P_1(t)\,dt$:

$$P_1(t)\,dt = \frac{1}{(k-1)!} p^k t^{k-1} e^{-pt}\,dt. \tag{27}$$

For $k > 2$, $P_1(t)$ increases first with an increasing first derivative then reaches an inflection point, and eventually a maximum. To the left of the maximum, the $P_1(t)$ curve has qualitatively a shape similar to the observed cancer incidence curves. Its initial increase is, however, not exponential. In principle it is easy to discriminate empirically between an exponential curve, as given by (10), and the left end of the curve (27). Thus we could decide between the hypothesis of a single fluctuation with variable probability and a multiple fluctuation with a constant probability. Actually the cancer incidence data are hardly accurate enough, and the individual empirical points are sufficiently scattered, to make such a decision at present doubtful. More accurate data are certainly needed.

It is, of course, possible to generalize the case of k fluctuations for a probability which varies with time.

The empirical value of the above considerations is very much reduced by the fact that in reality we do not deal with a uniform population. Consider, for instance, the case of a single fluctuation with constant probability. Let there be a distribution of p in a population of N_0 individuals so that the frequency of a p laying between p and $p + dp$ is

$$N(p)\,dp. \tag{28}$$

If equation (10) holds for a uniform population, then for a case of a population characterized by (28), we have

$$P_1(t) = \int_0^\infty N(p)\,p e^{-pt}\,dp, \tag{29}$$

which is different from (10). Similar considerations apply to other cases. In order to make use of the approach suggested here, it is essential to have a uniform population. This can be done with experimental animals such as mice. A difficulty, however, arises because of an insufficient number of individuals. Several hundred thousand mice

have been reared in laboratories for cancer research purposes. They are of a number of different genetically homogenous strains. But for *one* particular strain, the number of mice is of the order of a few thousands. The number of individuals per age groups is still less, and accurate statistics are thus impossible. In humans, we deal with populations of millions but with heterogenous material.

The cancer fluctuation discussed above may be conceived as due to the kinetic fluctuations of the number of molecules of some substance contained within the cell. If ν denotes the average number of molecules in an element of volume, then the probability that the *relative* accidental fluctuation of this number will be between δ and $\delta + d\delta$ is given by

$$W(\delta)\,d\delta = \sqrt{\frac{\nu}{2\pi}}\, e^{-\frac{\nu\delta^2}{2}}\, d\delta. \qquad (30)$$

The molecules in question may be those of some important catalyst which controls essential cell reactions. In order to throw a normal cell entirely out of balance, we would expect that δ should be rather large. In humans the probability of cancer incidence is of the order of 10^{-3} per person. An individual is composed of some 10^{13} cells. Hence the probability of a cancer fluctuation in a cell is of the order of 10^{-15}. Taking arbitrarily as a value of the relative fluctuation capable of producing cancer, one that lies between 0.5 and 0.6, we have $\delta = 0.5$; $d\delta = 0.1$. Introducing those values into (30) and putting $W(\delta)\,d\delta = 10^{-16}$, we find $\nu \sim 300$. We obtain the same order of magnitude for ν if we assume arbitrarily that any fluctuation larger than 0.5 will produce cancer. If we consider the fluctuation as occurring in the cell as a whole, and take the average volume of a cell as 10^{-8} cm^3, the above figure corresponds to a concentration of 5×10^{-11} mols per liter. If the critical fluctuation must occur only in a small part of the cell, say, 0.01 of its volume, then the concentration of the substance would be 5×10^{-9} mols per liter. Whatever it may be that is present in such small concentration, it must be present in much smaller concentrations in mice of such strains as show very high rates of spontaneous cancer incidence. This may provide a clue for experimental research.

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STEADY STATES IN RANDOM NETS: I

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A neural net is taken to consist of a semi-infinite chain of neurons with connections distributed according to a certain probability frequency of the lengths of the axones. If an input of excitation is "fed" into the net from an outside source, the statistical properties of the net determine a certain steady state output. The general functional relation between the input and the output is derived as an integral equation. For a certain type of probability distribution of connections, this equation is reducible to a differential equation. The latter can be solved by elementary methods for the output in terms of the input in general and for the input in terms of the output in special cases.

I. *The Single Semi-Infinite Chain.*

Consider a number of aggregates of neurons, $\mathcal{A}$, $\mathcal{B}$, $\mathcal{C}$, $\cdots$ such that each neuron of aggregate $\mathcal{A}$ sends an axone to a neuron of $\mathcal{B}$, effecting a mapping of $\mathcal{A}$ upon $\mathcal{B}$. Similarly, aggregate $\mathcal{B}$ is mapped on $\mathcal{C}$, etc. Such connections we shall call *mapping connections.* We may also have, in addition to the mappings $\mathcal{A} \to \mathcal{B} \to \mathcal{C} \cdots$, reciprocal mappings, $\cdots \mathcal{C} \to \mathcal{B} \to \mathcal{A}$.

Furthermore, suppose that a neuron of each aggregate sends an axone to a neuron in its own aggregate, effecting a *self*-mapping of the aggregate, e.g., $\mathcal{A} \to \mathcal{A}$. Such connections we shall call *association* connections.

Some initial state of excitation in a net consisting of such aggregates will then give rise to succeeding states in accordance with the statistical properties of the connections.

To fix ideas, suppose that each aggregate is a two-dimensional lamina, and let all the synaptic delays be equal and taken as a unit of time. The initial state of excitation, $F_0(\mathcal{A})$, may be thought of as a configuration of neurons in $\mathcal{A}$ firing at the instant $t = 0$. Because of the mapping connections, $\mathcal{A} \to \mathcal{B}$, a certain mapping of $F_0(\mathcal{A})$ will be fired in $\mathcal{B}$ at $t = 1$. Call this mapping $f_1(\mathcal{A}, \mathcal{B})$. If a reciprocal mapping, $\mathcal{B} \to \mathcal{A}$ exists, then a mapping of the configuration firing in $\mathcal{B}$ at $t = 1$, $f_2(\mathcal{B}, \mathcal{A})$ will fire in $\mathcal{A}$ at $t = 2$.

In the meantime, additional events will be happening in $\mathcal{A}$. Because of the association connections in $\mathcal{A}$, there will be a self-mapping of the configuration $F_0(\mathcal{A})$ to another configuration $f_1(\mathcal{A}, \mathcal{A})$

firing in $\mathcal{A}$ at $t = 1$. At the instant $t = 2$, therefore, the total configuration $F_2(\mathcal{A})$ firing in $\mathcal{A}$ will be the logical sum

$$f_2(\mathcal{A}, \mathcal{A}) + f_2(\mathcal{B}, \mathcal{A}).$$

And, in general,

$$\begin{aligned} F_i(\mathcal{A}) &= f_i(\mathcal{A}, \mathcal{A}) + f_i(\mathcal{B}, \mathcal{A}); \\ F_i(\mathcal{B}) &= f_i(\mathcal{B}, \mathcal{B}) + f_i(\mathcal{A}, \mathcal{B}), i \geqq 2. \end{aligned} \tag{1}$$

Analogous events will occur in a chain of aggregates with reciprocal mappings

$$\mathcal{A} \rightleftarrows \mathcal{B} \rightleftarrows C \rightleftarrows \cdots.$$

We might ask whether, under certain assumptions about the statistical properties of such nets, steady states can be established. We shall seek conditions for such steady states.

Consider a chain of neurons of semi-infinite length that is equivalent to the positive part of the real axis. Each neuron will be treated as a real point and designated by its coordinate $x (x \geqq 0)$. The association connections of the chain will be given by the distribution function, $K(x, \xi)$, that is to say, the probability that a neuron at x receives an axone from a neuron lying in the interval $(\xi, \xi + d\xi)$ is given by $K(x, \xi) d\xi$. Then the probability that a neuron at x receives an association axone at all will be given by

$$\int_0^\infty K(x, \xi) d\xi.$$

In general, we shall suppose that

$$\int_0^\infty K(x, \xi) d\xi < 1,$$

that is, not every neuron receives an association connection. But we will suppose that the neurons in our chain can be activated by an outside source. Furthermore, the threshold of each neuron will be taken to be equal to 1, and no neuron will receive more than one association connection. This is equivalent to saying that a neuron is sure to fire at t_i if a neuron which sends an association axone to it has fired at t_{i-1}, and that the probability of a neuron at x firing at t_i is equal to the fraction of neurons in the neighborhood of x firing at t_i.

By a *firing pattern*, $f_i(x)$, we shall mean a function of position, x, and of the instant, i, which indicates the probability that a neuron at x is firing at the instant $t = i$.

Suppose now that a firing pattern, $\phi_0(x)$, is applied to our chain

at $t = 0$. What will be the successive firing patterns of our chain? They will clearly be given by the following equations.

$$
\begin{aligned}
f_0(x) &= \phi_0(x), \\
f_1(x) &= \int_0^\infty K(x, \xi) f_0(\xi)\, d\xi, \\
f_2(x) &= \int_0^\infty K(x, \xi) f_1(\xi)\, d\xi \\
&= \int_0^\infty K(x, x_1) \int_0^\infty K(x_1 \xi) f_0(\xi)\, d\xi\, dx_1, \\
&\vdots \\
f_n(x) &= \int_0^\infty K(x, \xi) f_{n-1}(\xi)\, d\xi \\
&= \int_0^\infty K(x, x_{n-1}) \int_0^\infty \cdots \int_0^\infty K(x_2, x_1) \\
&\quad \cdot \int_0^\infty K(x_1, \xi) f_0(\xi)\, d\xi\, dx_1\, dx_2 \cdots dx_{n-1}.
\end{aligned}
\tag{2}
$$

These equations are a special case of equation (2) in the authors' previous paper (Shimbel and Rapoport, 1948).

Let us now suppose that $K(x, \xi)$ is given by

$$
\begin{aligned}
K(x, \xi) &= ke^{-k(x-\xi)} \qquad \text{for } x \geqslant \xi; \\
K(x, \xi) &= 0 \qquad\qquad\ \ \text{for } x < \xi.
\end{aligned}
\tag{3}
$$

In other words, the association connections of the chain go only to the right. Such a chain would arise if, when the axones grew, the probability of an axone's acquiring a given length before it was "captured" by a neuron would be analogous to the probability of a given free path length for a gas molecule.

Under this assumption, the neuron at $x = 0$ receives no association connection. Any other neuron x may receive a connection from some neuron to the left of it, the closest neurons being the most probable sources. The probability of a neuron at x receiving a connection at all is given, in view of equation (3), by

$$
\int_0^x ke^{k(\xi - x)}\, d\xi = 1 - e^{-kx}. \tag{4}
$$

This probability increases with x and approaches 1 asymptotically.

If an initial firing pattern $\phi_0(x)$ is now impressed on the chain, the successive states will be given by

$$\begin{aligned} f_0(x) &= \phi_0(x), \\ f_1(x) &= \int_0^x k e^{k(\xi - x)} f_0(\xi)\, d\xi = e^{-kx} \int_0^x k e^{k\xi} f_0(\xi)\, d\xi, \\ &\cdots \\ f_n(x) &= e^{-kx} \int_0^x k e^{k\xi} f_{n-1}(\xi)\, d\xi. \end{aligned} \tag{5}$$

In particular, if $f_0(x) = f_0$, a constant, these equations reduce to the following

$$\begin{aligned} f_1(x) &= f_0(1 - e^{-kx}), \\ f_2(x) &= f_0[1 - e^{-kx}(1 + kx)], \\ &\cdots \\ f_n(x) &= f_0 \left\{ 1 - e^{-kx} \left[1 + kx + \frac{k^2x^2}{2!} + \cdots \frac{k^{n-1}x^{n-1}}{(n-1)!} \right] \right\}. \end{aligned} \tag{6}$$

All the distributions are monotone increasing and have a negative second derivative with respect to x. All of them approach f_0 asymptotically. The limit of the probability of firing as $t \to \infty$ is zero for each neuron, but not uniformly with respect to x.

Now suppose a firing pattern $\phi(x)$, constant with respect to time, impressed on the net by an outside source. We shall call such a pattern (impressed at each instant) the *input*. The equations of successive states then become

$$f_n(x) = \phi(x) + [1 - \phi(x)] \int_0^\infty K(x, \xi) f_{n-1}(\xi)\, d\xi. \tag{7}$$

The factor $[1 - \phi(x)]$ denotes the non-additivity of the probabilities that a neuron is firing because of the outside source or that it is firing because of an association connection with a firing neuron.

A necessary and sufficient condition for a steady state is then given by a linear integral equation

$$f(x) = \phi(x) + [1 - \phi(x)] \int_0^\infty K(x, \xi) f(\xi) d\xi . \tag{8}$$

The question whether a given input $\phi(x)$ will actually lead to a steady state must be considered separately. If such a steady state is actually reached, we shall refer to it as the *output.*

Imposing condition (3) on $K(x, \xi)$ of equation (8), we obtain

$$f(x) = \phi(x) + [1 - \phi(x)] \int_0^x k e^{k(\xi - x)} f(\xi)\, d\xi . \tag{9}$$

This type of integral equation (with separable kernel) is especially simple, since it can be transformed into a linear differential equation of the first order. Differentiating both sides of equation (9) with respect to x, we obtain

$$f'(x) = \phi'(x) + F'(x) \int_0^x k e^{k\xi} f(\xi) d\xi + kf(x) - k\phi(x) f(x), \tag{10}$$

where $F(x) \equiv e^{-kx}[1 - \phi(x)]$ and hence

$$F'(x) = e^{-kx}[k\phi(x) - k - \phi'(x)] .$$

Substituting for

$$\int_0^x k e^{k\xi} f(\xi) d\xi$$

its value $[f(x) - \phi(x)]/F(x)$ obtained from equation (9), we obtain

$$\begin{aligned} f'(x) = \phi'(x) \frac{F'(x)}{F(x)} [f(x) - \phi(x)] \\ + kf(x) - k\phi(x) f(x), \end{aligned} \tag{11}$$

and, finally, after elementary substitutions and reductions

$$f' - \phi f' = \phi' - f\phi' + k\phi - k\phi^2 - k\phi f + k\phi^2 f . \tag{12}$$

This equation can be considered either as a differential equation in f with ϕ a known function or a differential equation in ϕ with f a known function. Taken as the former, it can be written as

$$f'(1 - \phi) + f(\phi' + k\phi - k\phi^2) = \phi' + k\phi - k\phi^2 . \tag{13}$$

Theorem 1. *The output* $f \equiv 1$ *if and only if the input* $\phi(x) \equiv 1$.

Proof. Substituting $f \equiv 1$ into equation (9) we obtain

$$1 = \phi(x) + [1 - \phi(x)][1 - e^{-kx}]$$

$$1 = \phi(x) + 1 - e^{-kx} - \phi(x) + \phi(x)e^{-kx}$$

$$e^{-kx}[\phi(x) - 1] = 0$$

$$\phi(x) = 1 .$$

The converse is trivial.

Theorem 2. *The successive states* $f_i(x)$ *are non-decreasing with respect to time, that is,* $f_j(x) \geqq f_i(x)$ *for all* x.

Proof. The conclusion obviously holds for $j = 1$. We shall make an induction on j. Imposing condition (3) on equation (7) we obtain

$$f_n(x) = \phi(x) + [1 - \phi(x)] \int_0^x k e^{k(\xi - x)} f_{n-1}(\xi)\, d\xi ; \tag{14}$$

$$f_{n+1}(x) = \phi(x) + [1 - \phi(x)] \int_0^x k e^{k(\xi - x)} f_n(\xi)\, d\xi . \tag{15}$$

Subtracting equation (15) from (14), we have

$$f_n(x) - f_{n+1}(x) = [1 - \phi(x)] \int_0^x k e^{k(\xi - x)} [f_{n-1}(\xi) - f_n(\xi)]\, d\xi . \tag{16}$$

Since $\phi(x)$ is a probability function, $0 \leqq \phi(x) \leqq 1$. Moreover, $ke^{k(\xi - x)} > 0$ for all x. Hence, if $f_{n-1}(\xi) - f_n(\xi) \geqq 0$, so is $f_n(x) - f_{n+1}(x)$. But this completes the induction. Hence the theorem is proved.

Theorem 3. *If* $\phi(x)$ *and* $f(x)$ *are taken to be differentiable functions of* x, *then the steady state* $f(x)$ *actually represents an output for the given input* $\phi(x)$.

Proof. Since the steady state is given by a solution of a linear differential equation of the first order, it is unique for a given input. Moreover, the successive states are non-decreasing and have an upper bound $f = 1$. Therefore, they approach a limiting function, and this cannot be $f = 1$, unless $\phi = 1$. The successive states f_i are uniformly continuous in any finite interval; therefore, their limit is continuous. Hence, it must be the unique solution of equation (13). This proves the theorem.

If we discard the trivial case $\phi = 1$, we may divide both sides of equation (13) by $(1 - \phi)$ and obtain

$$f' + f\left(\frac{\phi'}{1 - \phi} + k\phi\right) = \frac{\phi'}{1 - \phi} + k\phi . \tag{17}$$

Let us denote $\phi'/(1-\phi) + k\phi$ by Φ. Then the solution of equation (17) is

$$f(x) = e^{-\int_0^x \Phi dx}\left[\int_0^x e^{\int_0^x \Phi dx}\Phi dx + \phi(0)\right] \tag{18}$$

$$= 1 - [1-\phi(0)]\, e^{-\int_0^x \Phi dx}.$$

Substituting for Φ its value in terms of ϕ, we obtain

$$\int_0^x \Phi dx = \int_0^x \left(\frac{\phi'}{1-\phi} + k\phi\right) dx = \log\frac{1-\phi(0)}{1-\phi(x)} + k\int_0^x \phi dx, \tag{19}$$

$$e^{-\int_0^x \Phi dx} = \frac{1-\phi(x)}{1-\phi(0)}\, e^{-k\int_0^x \phi dx},$$

and finally

$$f(x) = 1 - [1-\phi(x)]\, e^{-k\int_0^x \phi(x)dx}.$$

We summarize this result in

Theorem 4. *Let the input be* $\phi(x)$, *a differentiable function of* x. *Then the output will be*

$$f(x) = 1 - [1-\phi(x)]\, e^{-k\int_0^x \phi(x)dx}. \tag{20}$$

Equation (20) gives the output for any input which is a differentiable function of x. Theorem 3 insures the existence of such an output, i.e., that the steady state is actually reached.

Let us now consider the inverse problem of finding an input which will assure a prescribed output. Equation (9) can be solved directly for $\phi(x)$ in terms of $f(x)$, namely,

$$\phi(x) = \frac{f(x) - \int_0^x ke^{k(\xi-x)} f(\xi)\, d\xi}{1 - \int_0^x ke^{k(\xi-x)} f(\xi)\, d\xi}. \tag{21}$$

If $f(x)$ is explicitly given, $\phi(x)$ can be obtained by quadratures. However it may be interesting to consider problems where f is given not as a function of x but as a function of ϕ. In other words, we wish to investigate the input where a certain functional relation is given between the output and the input. Certain special cases are easily solvable and will be given here.

In particular, let the output $f(x) = f$, a constant. Rewriting equation (12) as a differential equation in ϕ, we have

$$\phi'(1-f) - k\phi^2(1-f) + k\phi(1-f) = 0. \tag{22}$$

Since we have already disposed of the case $f = 1$ in Theorem 1, we can suppose that $1 - f \neq 0$. Then we may write equation (22) as

$$\phi' - k\phi^2 + k\phi = 0; \tag{23}$$

$$\frac{d\phi}{\phi^2 - \phi} = \frac{-d\phi}{\phi} - \frac{d\phi}{1-\phi} = kdx. \tag{24}$$

Integrating equation (24), we obtain

$$\log \frac{C\phi}{1-\phi} = -kx, \tag{25}$$

where C is a constant of integration. Since the neuron at $x = 0$ fires only because of the input, we must have $f = \phi(0)$, $Cf = 1 - f$, $C = (1 - f)/f$, and consequently

$$\begin{aligned} \frac{(1-f)\phi(x)}{f[1-\phi(x)]} &= e^{-kx}; \\ \phi(x) &= \frac{fe^{-kx}}{1-f+fe^{-kx}}. \end{aligned} \tag{26}$$

As another special case, consider the output which is a "mirror image" of the input, that is, $f(x) = 1 - \phi(x)$. Then equation (22) reduces to

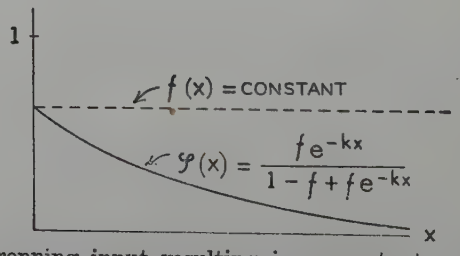

FIGURE 1. A dropping input resulting in a constant output, the difference being built up by the increasing association connections along the chain.

$$\phi' = -k\phi^2(1-\phi); \tag{27}$$

$$\frac{d\phi}{\phi^2(1-\phi)} = -kdx. \tag{28}$$

Breaking the left-hand side of (28) into partial fractions, we obtain

$$\frac{d\phi}{\phi^2} + \frac{d\phi}{\phi} + \frac{d\phi}{1-\phi} = -kdx, \tag{29}$$

and upon integrating

$$\log\frac{1-\phi}{\phi} + \frac{1}{\phi} + A = kx. \tag{30}$$

To evaluate the constant of integration, A, we note that $\phi(0) = f(0) = 1 - \phi(0)$, hence, $\phi(0) = 1/2$. Substituting this value into (30) we obtain

$$x = \frac{1}{k}\left[\log\frac{\phi}{1-\phi} + \frac{1}{\phi} - 2\right]. \tag{31}$$

This equation is transcendental in ϕ but is solved for x. Its graph is shown in Figure 2.

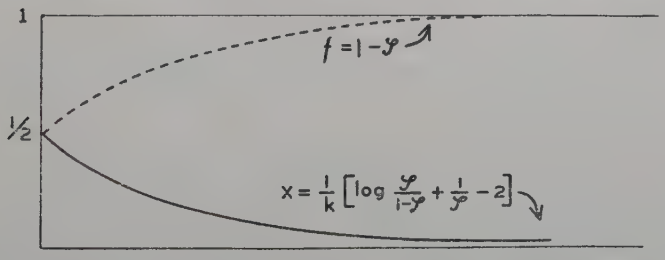

FIGURE 2. The "mirror image" case. A dropping input associated with a symmetrically rising output.

If any functional relation is imposed on the input and the output functions, for example, $f = F(\phi)$ where F is a differentiable function of ϕ, equation (12) can be formally solved by separation of variables. In fact, the equation then assumes this form

$$\frac{d\phi[F(\phi) + F'(\phi) - \phi F'(\phi) - 1]}{\phi[1-F(\phi)][1-\phi]} = kdx, \tag{32}$$

which can be solved by a quadrature if the form of $F(\phi)$ is known.

However, the only solutions which are significant from the point of view of the random net theory are those for which $0 \leqq \phi(x) \leqq 1$

and $0 \leqq f(x) \leqq 1$ for all x. If a solution of (32) yields either $\phi(x)$ or $f(x)$ which violate the inequalities mentioned above, we must conclude that the functional condition $f = F(\phi)$ cannot be fulfilled for our net. An example of such a situation is the following.

Suppose we wish our output to be *similar* to our input, i.e., to satisfy the condition $f = C\,\phi$ where C is a constant. By Theorem 1, we must have $C \geqq 1$, and from equation (12) it is evident that $C = 1$ if, and only if, $f = \phi = 0$. This case being trivial, we shall suppose that $C > 1$. Then equation (32) reduces to

$$\frac{d\,\phi(C-1)}{\phi(1-C\,\phi)\,(1-\phi)} = k dx. \tag{33}$$

The formal solution of equation (33) is given by

$$\frac{1}{k}\log\left[\frac{A\,\phi^{C-1}(1-\phi)}{(1-C\,\phi)^{C}}\right] = x. \tag{34}$$

But we must have for $x = 0$, $f = C\,\phi = \phi$. Since $C \neq 1$, $\phi(0)$ must be zero. But for ϕ very close to zero, x becomes negatively large, and therefore the solution is meaningless.

One might raise the question concerning the class of functions F, such that the condition $f = F(\phi)$ may be imposed on the net described here.

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STEADY STATES IN RANDOM NETS: II

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Two semi-infinite chains are considered interacting as random nets. Conditions for steady state are derived for the cases of cross-excitatory and cross-inhibitory association connections. In the cross-inhibitory case a unique non-trivial self-reproducing steady state is shown to exist.

As an example of interacting random nets, we shall examine two semi-infinite chains of the type treated in Steady States in Random Nets: I (Rapoport and Shimbel, 1948), hereafter referred to as I.

We shall suppose that the chains send association connections to each other (for a definition of association connections, see I). A neuron in either chain can now fire for any of the following reasons:

1. It can be excited by an outside source.

2. It can be excited by an association connection with a firing neuron of its own chain.

3. It can be excited by an association connection with a firing neuron of the other chain.

Let the chains be denoted by $\mathcal{F}$ and $\mathcal{G}$ and let them be "fed" by the respective patterns $\phi(x)$ and $\gamma(x)$ where these functions denote the probability of firing of the neuron at x. The variable x, as in I, denotes the distance from the beginning of each of the two semi-infinite chains. Then, if $K(x, \xi)$ denotes the probability of connection of the neuron at x to a neuron at ξ of either chain, the equations for the resulting firing patterns, $f_n(x)$ and $g_n(x)$ will be given by

$$\begin{aligned} f_n(x) &= 1 - [1-\phi(x)]\left[1 - \int_0^\infty K(x,\xi) g_{n-1}(\xi)\, d\xi\right]\left[1 \right. \\ &\quad \left. - \int_0^\infty K(x,\xi) f_{n-1}(\xi)\, d\xi\right] \\ g_n(x) &= 1 - [1-\gamma(x)]\left[1 - \int_0^\infty K(x,\xi) f_{n-1}(\xi)\, d\xi\right]\left[1 \right. \\ &\quad \left. - \int_0^\infty K(x,\xi) g_{n-1}(\xi)\, d\xi\right]. \end{aligned} \tag{1}$$

Each factor in brackets expresses the probability that the neuron at x does *not* fire because of either the outside source or one of the association connections. Hence the product of these factors subtracted from unity gives the probability that the neuron at x does fire at $t = n$.

For steady states in $\mathcal{J}$ and $\mathcal{G}$, equations (1) reduce to a system of non-linear integral equations

$$\begin{aligned} f(x) &= 1 - [1 - \phi(x)]\left[\, 1 - \int_0^\infty K(x,\xi) g(\xi)\, d\xi \,\right]\left[\, 1 \right. \\ &\quad \left. - \int_0^\infty K(x,\xi) f(\xi)\, d\xi \,\right] \\ g(x) &= 1 - [1 - \gamma(x)]\left[\, 1 - \int_0^\infty K(x,\xi) f(\xi)\, d\xi \,\right]\left[\, 1 \right. \\ &\quad \left. - \int_0^\infty K(x,\xi) g(\xi)\, d\xi \,\right]. \end{aligned} \tag{2}$$

In this paper we shall treat only the symmetric case where $\phi(x) = \gamma(x)$ and hence $f(x) = g(x)$. We shall denote

$$\int_0^\infty K(x,\xi) f(\xi)\, d\xi$$

by $F(x)$ and will take our kernel to be separable as in I, so that

$$F(x) = \int_0^x k e^{k(\xi - x)} f(\xi)\, d\xi . \tag{3}$$

Note that $F(x)$ satisfies the differential equation

$$F'(x) = k[f(x) - F(x)] . \tag{4}$$

For the symmetric case, equations (2) reduce to

$$f(x) = 1 - [1 - \phi(x)][1 - F(x)]^2 . \tag{5}$$

Differentiating both sides of (5), we obtain

$$f' = 2(1 - F)(1 - \phi) F' + \phi'(1 - F)^2 . \tag{6}$$

Furthermore, solving equation (5) for F, we get

$$F = 1 - \sqrt{\frac{1 - f}{1 - \phi}} . \tag{7}$$

Substituting the value of F from (7) into (4), we get

$$F' = k\left[\sqrt{\frac{1-f}{1-\phi}} - (1-f)\right]. \tag{8}$$

Finally, substituting (8) and (7) into (6), we derive the following differential equation for f

$$f' = 2k\sqrt{(1-f)(1-\phi)}\left[\sqrt{\frac{1-f}{1-\phi}} - (1-f)\right] + \phi'\frac{1-f}{1-\phi}. \tag{9}$$

Denoting $1-f$ by $\bar{f}$ and $1-\phi$ by $\bar{\phi}$, we obtain equation (9) in a simpler form, namely,

$$\bar{f}' + \bar{f}(2k - \bar{\phi}'/\bar{\phi}) = 2k\bar{f}^{3/2}\bar{\phi}^{1/2}. \tag{10}$$

This differential equation is non-linear in $\bar{f}$, but is easily solvable by the substitution $z = (\bar{f})^{-1/2}$. This change of variable reduces equation (10) to

$$z' - z(k - \bar{\phi}'/2\bar{\phi}) = -k\bar{\phi}^{1/2}, \tag{11}$$

which is linear in z and has for solution

$$z = (\bar{\phi})^{-1/2} e^{kx}\left[-k\int_0^x e^{-kx}\bar{\phi}(x)\,dx + C\right]. \tag{12}$$

Since the neuron at $x = 0$ has no association connections, we must have $f(0) = \phi(0)$. Hence $z(0) = [\phi(0)]^{-1/2}$. Therefore

$$C = [\bar{\phi}(0)/\phi(0)]^{1/2}.$$

Resubstituting $(1-f)^{-1/2}$ for z, we obtain finally as the solution of equation (9)

$$f(x) = 1 - \frac{1-\phi(x)}{e^{2kx}\left[\left(\frac{1-(0)}{\phi(0)}\right)^{1/2} - k\int_0^x e^{-kx}(1-\phi(x))\,dx\right]^2}. \tag{13}$$

We shall next consider a "cross-inhibitory" case. Let now the association connections of $\mathcal{I}$ on $\mathcal{G}$ and of $\mathcal{G}$ on $\mathcal{I}$ be of inhibitory kind, that is, if a neuron at x receives a stimulus at $t = n$ from a neuron of the *other* chain, it will not fire no matter what other stimuli it receives. The steady state equation in this case will be

$$f = [1 - (1-\phi)(1-F)](1-F). \tag{14}$$

The equation states that a neuron at x fires if it receives a stimulus from either the outside source (probability ϕ) or from an association connection from its own chain (probability F), *provided* it does not

at the same time receive a stimulus from an association connection from the other chain (probability $(1-F)$).

Differentiating both sides of equation (14), we obtain

$$f' = -F' + \phi'(1-F)^2 + 2(1-\phi)(1-F)F', \tag{15}$$

which, upon substituting of the value of F' from (4), becomes

$$f' = kF - kf + \phi'(1-F)^2 + 2k(f-F)(1-\phi)(1-F). \tag{16}$$

However, equation (14) solved for F yields

$$F = 1 - \frac{1 \pm \sqrt{1-4f+4f\phi}}{2(1-\phi)}. \tag{17}$$

These values substituted into (16) reduce the latter to two differential equations which determine f as a function of ϕ. The equations are non-linear in f and in ϕ, and no attempt will be made here to solve them or to obtain any information as to the significance of the ambiguity of equation (17). We shall only investigate the special case where $f = \phi$. That is to say, we seek an input function $\phi(x)$ such that in the steady state the output function $f(x)$ shall be equal to it.

This situation was not considered in any of the cases treated in I, nor in the cross-excitatory case of the present paper, because it is evident that without inhibitory connections, the only self-reproducing steady states are the trival ones, $\phi = 0$ and $\phi = 1$.

Assuming $f = \phi$ reduces equation (17) to

$$F = 1 - \frac{1+(1-2\phi)}{2(1-\phi)} = 0, \tag{18}$$

or to

$$F = 1 - \frac{1-(1-2\phi)}{2(1-\phi)} = \frac{1-2\phi}{1-\phi}. \tag{19}$$

Discarding the trivial case (18), which is equivalent to assuming that there are no association connections at all, we proceed to derive our equation of the steady state on the basis of (19).

Equation (16) reduces to

$$\frac{(1-2\phi)\,d\phi}{(1-\phi)(\phi^2-3\phi+1)} = k(1-2\phi)\,dx. \tag{20}$$

From equation (20) it is immediately evident that the constant input $\phi = 1/2$ satisfies the differential equation of the steady state.

It also satisfies the boundary condition, since by definition of $F(x)$, we must have $F(0) = 0$, which substituted into equation (19) gives $\phi(0) = 1/2$. It remains to investigate whether the constant input $\phi = 1/2$ is the only self-reproducing input under the conditions of cross-inhibitory association connections considered here.

Discarding the solution $\phi = 1/2$, we obtain from (20), the differential equation

$$\frac{d\phi}{(1-\phi)(\phi^2-3\phi+1)} = kdx,$$

which, upon integration by the method of partial fractions, yields the general solution

$$\begin{aligned} &\log(1-\phi) - 1/2\log(r_1-\phi) - 1/2\log(\phi-r_2) \\ &+\frac{1}{2\sqrt{5}}\log(r_1-\phi) - \frac{1}{2\sqrt{5}}\log(\phi-r_2) + \log A = kx, \end{aligned} \tag{21}$$

where $r_1 = 3/2 + \sqrt{5}/2$, $r_2 = 3/2 - \sqrt{5}/2$, and A is a constant of integration. Equation (21) may be rewritten as

$$\log\left[\frac{A(1-\phi)}{(r_1-\phi)^{\frac{\sqrt{5}-1}{2}}(\phi-r_2)^{\frac{\sqrt{5}+1}{2}}}\right] = kx. \tag{22}$$

The boundary condition $\phi(0) = 1/2$ fixes the constant A. The curve starts at $\phi(0) = 1/2$ and is monotone decreasing, approaching the line $\phi = r_2 \sim 0.39$ asymptotically as shown in Figure 1.

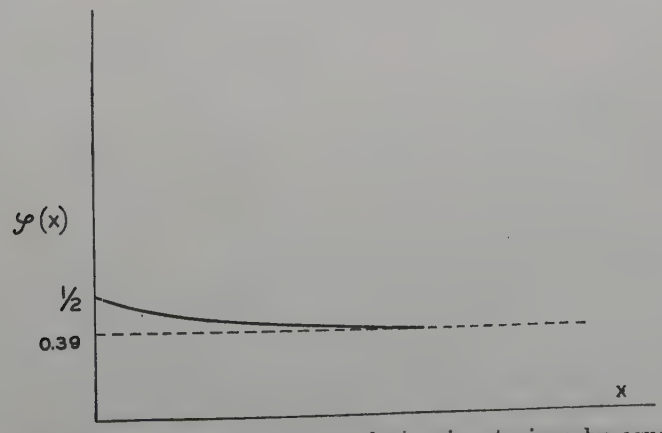

FIGURE 1. The non-constant self-reproducing input given by equation (22).

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BOOK REVIEW

JOHN H. NORTHROP, MOSES KUNITZ AND ROGER M. HERRIOTT. *Crystalline Enzymes.* Second edition, 1948. xxi + 352 pp. New York: Columbia University Press. $7.50.

This new edition of *Crystalline Enzymes*, which has been extensively revised and enlarged, follows its predecessor after nine years. The First Edition was based upon the Jesup Lectures given in the spring of 1938 at which time ten enzymes had been crystallized and identified as proteins. A list of thirty-nine crystalline enzymes is presented in the new edition.

At present, the identity of the crystalline protein and the enzyme seems to be an inescapable fact and is seldom questioned; for those who still have doubts, cogent arguments (whether or not explicit) are to be found in practically every chapter of this book. New material has been included in all chapters. Added topics include chapters on two "new" enzymes (ribonuclease and hexokinase), a chapter on crystalline diphtheria antitoxin, and (appropriately in view of the work carried out during the war and still being actively pursued) a chapter dealing with the reaction of mustard gas with proteins and enzymes.

The subject matter of this book, as in the case of the First Edition, is expressly restricted to results of research done at Rockefeller Institute and subjects closely related to these results; consequently, the enzymes discussed are, with the exception of ribonuclease and hexokinase, proteolytic enzymes. Included also are the precursors and inhibitors of the various enzymes, bacteriophage, and diphtheria antitoxin.

Rather than impair the continuity of the text with a statement of detailed procedure, the authors discuss the stepwise procedure for isolation, fractionation, and crystallization of the enzymes in an extensive Appendix. The book is excellently documented with graphs and figures and no less than 500 references which are given in a separate bibliography.

While manifestly this book will be of greatest interest to those whose business it is to isolate and study enzymes, it describes methods and techniques which now concern more workers than might at first be thought. The original crystallization of an enzyme, in general, presents formidable technical difficulties and is a task from which one might shrink with no sense of false modesty. The availability of reproducible methods for obtaining highly purified or crystalline enzymes, however, has led to their widespread use. Today it is not unusual for an investigator to have on hand an array of such preparations to be used as test systems incidental to his major problem. The use of highly purified enzymes for the analytical determination of various metabolites has rapidly increased in recent years.

Crystalline Enzymes contains much material which is of quite general interest; for example, the discussion of the equilibrium between native and denatured protein and the thermal analysis of this equilibrium. This concept of a *reversible* shift from native protein to denatured protein has made its appearance explicitly in the more recent formulations of enzymatic rate processes in

their dependence upon temperature and is repeatedly invoked in discussions of temperature effects on living cells.

Other features of rather general interest and use include an excellent account (given in the Appendix) of the porous diaphram method for the determination of diffusion coefficients. A discussion is given of relevant information, other than molecular weight and diffusion coefficient, which may be obtained from diffusion studies; the necessary equations are derived and the methodology is given in some detail. Another valuable discussion deals with the appliication of Gibb's phase rule to protein solutions. Results of such studies are given throughout the text and the Appendix contains a discussion of the theory involved and experimental methods employed. The phase rule is the essence of simplicity as is, in principle, its application to physicochemical systems. In the study of protein solutions, however, there are several factors to be considered and matters are not always simple. One usually has to deal with systems of four or more components, viz., water, salt, acid, and protein. While it is true that an additional component, whose concentration is fixed, introduces no change in the number of degrees of freedom, it is necessary, in practice, to examine the question of the extent to which the conditions of constant acidity and salt concentration may be met when the amount of solid protein is varied. Just such considerations are discussed in a lucid manner. Also the various cases which arise (mixture of proteins, solid solution, etc.) are brought together and discussed in a valuable presentation.

Most interesting is the final chapter of the book wherein a general discussion of protein synthesis is presented. The general theme developed is that the formation of viruses, the elaboration of enzymes, and the formation of "normal proteins" are but aspects of the general problem of protein synthesis. The possible mechanisms of synthesis are placed in two classes: shift of equilibrium by change in concentration, or removal of product and coupled reactions. In the discussion of the various aspects of these types of reactions two points, which heretofore have received but scant attention, are stressed: the formation of native protein in contradistinction to denatured protein and the possibility of accounting to some extent for the specificity of synthesis on the basis of the chemical properties of the protein itself. Both points warrant some comment.

It is stated that most native proteins are very slowly hydrolyzed and that the possibility is, therefore, open that the first step in the hydrolysis of native protein is the denaturation of the protein. Evidence is also cited to indicate that globular proteins are not hydrolyzed by trypsin unless they are in the denatured form but that fibrous proteins are hydrolyzed at about the same rate in the native and denatured forms. The proposition is then forwarded that, "If enzymatic hydrolysis does require preliminary denaturation, then it could be assumed that *native* proteins can be synthesized without adding energy, i.e., by a purely catalytic reaction. Energy is required to denature the protein which then hydrolyzes with the liberation of energy." It must be granted that the experimental fact that the equilibrium protein $\rightleftarrows$ amino acids is far to the right is established only for the case of denatured protein; this is a fact not previously invoked in the discussion of the energetics of protein synthesis and deserves some attention. It also seems clear, however, that the ΔF_0's of the syntheses of native and denatured proteins can differ only by the ΔF_0 of the denaturation. In cases where the data is available, the ΔF_0 of denaturation is rather small and could not be an important factor in these cases.

The interesting suggestion is made that protein synthesis may be specific in the sense that ordinary chemical reactions are specific, viz., only one or a small

number of the *possible* reaction products actually appears. The example given is that of the formation of *NaCl* and H_2O from *NaOH* and *HCl*. Statistically a great number of products are possible, but only *NaCl* and H_2O are stable under the usual conditions. This point of view is similar to that adopted in the statistical mechanical treatment of chemical equilibria: that part of phase space which is reached but slowly is regarded as non-existent. Here, however, the system is considered to be "inhibited" on a *rate* basis. Obviously a system is never in equilibrium with respect to every possible reaction; only those states rapidly attained are considered. Whatever the control of specificity in protein syntheses may be, it is exceedingly stringent and would seem to require some special device. For example, if a protein is considered to consist of 288 amino acids equally distributed among twelve different amino acids, then if *one* molecule of every possible isomer existed, the total mass would exceed the mass of the earth by a factor of 10^{253}. This calculation, due to Schlenk, does not include configurational isomerism but clearly shows, even with this restriction, the physical impossibility of the existence of a single molecule of each isomer.

The authors finally suggest a working hypothesis for protein synthesis. Briefly, they consider that the first stage is the formation of one or more "type" precursor or "proteinogen" which exhibits organ and species specificity. The proteinogen is considered to be similar to the ur-protein suggested by Alcock in 1936; its formation requires energy and is autocatalytic. The second step is the (spontaneous) formation of the individual proteins from the proteinogens. On the basis of this hypothesis, the authors discuss the formation of normal protein, adaptive enzymes, antibodies, and viruses.

Although the hypothesis and its basis are not wholly acceptable to this reviewer, they embody features which are logically attractive and of great interest; the spirit in which this hypothesis is forwarded will be appreciated by the readers of this journal.

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